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**The effect of transdermal opioids on patient healthcare utilisation:
comparison with oral opioids in the treatment of persistent (non-
cancer) pain in North West Tasmania**

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Doctor of Philosophy

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Declaration

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Statement of ethical conduct

The research associated with this thesis abides by the guidelines of the Human Research Ethics Committee (Tasmania) Network; approval number H0009695.



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List of Abbreviations

ABS	Australian Bureau of Statistics
ARIA	Accessibility / Remoteness Index of Australia
ASGC	Australian Standard Geographical Classification
ATC	Anatomical Therapeutic Chemical
CAM	Complementary and Alternative Medicine
CNCP	Chronic Non-Cancer Pain
DEM	Department of Emergency Medicine
DSU	Day Surgery Unit
DHHS	Department of Health and Human Services (Tasmania)
E2SFCA	Enhanced Two-Step Floating Catchment Area
ER	Extended Release
GEE	General Estimating Equations
GP	General Practitioner)
HREC	Human Research Ethics Committee (Tasmania)
IASP	International Association for the Study of Pain
IDU	Injecting Drug User
IM	Intramuscular
IR	Immediate Release
IV	Intravenous
LGA	Local Government Area
MA	Monthly S4 Analgesia
MAD	Monthly Antidepressant
MBZ	Monthly Benzodiazepine
MHC	Monthly Healthcare Contact
MHE	Monthly Healthcare Expense
MHT	Monthly Healthcare Time
MIR	Monthly Immediate Release Opioid
MPC	Multidisciplinary Pain Clinic
MRI	Magnetic Resonance Imaging
MS	Morphine Sulphate

NDRAC	National Drug and Alcohol Research Centre
NMDA	N-Methyl-D-Aspartate
NSAID	Non-Steroidal Anti-Inflammatory Drug
OCR	Oral Controlled Release
OTC	Over the Counter
OVDO	Olympic Victor's Dark Ointment
PBS	Pharmaceutical Benefits Scheme
POA	Postal Area
PSB	Pharmaceutical Services Branch (Tasmania)
RA	Remoteness area
SC	Subcutaneous
SD	Statistical Division
SSNI	Selective Noradrenalin Reuptake inhibitor
SSRI	Selective serotonin Reuptake inhibitor
TAC	Telephone Area Code
TCA	Tri-Cyclic Antidepressant
TGA	Therapeutic Goods Administration
TD	Transdermal

Publications arising from the work described in this thesis

Henshaw JS. Do transdermal opioids reduce healthcare use in an Australian rural pain population? A comparison with oral opioids. *J Opioid Manag* 2011;7(2):135-44.

Henshaw JS, Walker, J, Geraghty,D. Do transdermal opioids affect the personal socio-economic costs of healthcare access in an Australian rural pain population? A comparison with oral opioids. *J Opioid Manag* 2012;8(2):126-132.

Henshaw JS, Walker, J, Geraghty,D The effect of transdermal opioid use on 'breakthrough' opioid and sedative prescribing for rural pain patients in North West Tasmania; a longitudinal study. *J Pain Research* (in press).

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Abstract

'These skin patch patients seem happier'.

This chance remark from the pain clinic nurse, in 2007, was the seed that grew into this study. Increasingly, patients prescribed transdermal opioids, were being referred to the clinic. These medicines became available in North West Tasmania during the previous year. Until then, oral opioids were the mainstay of intractable chronic non-cancer pain (CNCP) treatment.

The north west of Tasmania is a predominantly rural area of 22,492 square kilometres, with a population, in 2008, of 111,100 people. Access to healthcare is often more difficult here, than in with the major population centres, due to the 'tyranny of distance' and reduced specialist medical and allied health services available locally

This pain clinic, based at the NW Regional Hospital, opened its doors in 2005. The previous ad hoc system, provided by the anaesthetic department acute pain service, had become overwhelmed by the persistent pain workload. The catalyst for this was the well publicised withdrawal of VioxxTM (rofecoxib) in 2004, highlighting the potential long term cardiovascular adverse effects of both cyclo-oxygenase-2 selective inhibitors (coxibs) and standard non steroidal anti-inflammatory drugs (NSAIDs). Quickly, opioid analgesics were replacing coxibs

and NSAIDs for the management of the painful musculoskeletal degenerative changes associated with aging, as their long term safety profile was predictable.

Long-term opioid management is complex, in achieving a balance between efficacy of pain relief and minimisation of harm. Efficacy of pain relief requires stable therapeutic levels of medication, which may be difficult to achieve even with long acting oral opioid preparations. Minimisation of harm requires the reduction of untoward patient effects and the prevention of opioid diversion to the community. This requires significant healthcare resources to optimise patient care. Our newly arriving patients who were being treated with transdermal opioids seemed to be following a simpler path.

If patients seemed happier with these transdermal medicines, they might need less frequent healthcare access. This concept framed the study. There was no published data available on the effect of the route of opioid analgesia, on healthcare utilisation, by persistent pain patients. This was the first Australian study to measure this in a rural context.

This prospective longitudinal study compared 1804 months of healthcare activity by 198 subjects using oral or transdermal opioids. Subjects recorded details of all their 'out of home' healthcare contacts, together with the type, route, and dosage, of their opioid medication(s).

There is a personal socioeconomic cost involved in accessing healthcare, and this increases in rural areas. Pain patients may use additional analgesics with their opioid analgesics. These related issues were assessed, as any benefit from reduced healthcare activity would likely be lost if patient costs, or their need for additional analgesics, increased.

The study revealed that General Practitioner contacts were reduced significantly, by one fifth, and there was a trend towards less total healthcare activity, by patients using transdermal opioids. Pharmacy visits remained unaffected, probably as a consequence of the regularly repeated dispensing of all subject medications.

Their personal socioeconomic costs involved remained unchanged. This included all out of pocket healthcare and travel expenses, together with the time taken to access this healthcare. On average, the subjects spent five hours each month and had out of pocket expenses of over one hundred dollars to do this.

Additional analgesic and sedative use was unchanged, but there was a trend towards reduced use of short acting opioid analgesics for 'breakthrough' pain. Whether some patients have individual characteristics that enhance their response to the 'steady state' delivery of opioid medication by the transdermal route is currently unknown.

If the risk of diversion is a consideration in prescribing opioid analgesics for rural pain patients then, at present, transdermal opioids are the safer option. If this leads to a reduction in the prevalence of opioid diversion in NW Tasmania, there are considerable economic benefits, both from a reduction in self-harm, and from drug enforcement costs.

In NW Tasmania, transdermal opioids do seem to offer a benefit to patients compared to oral opioids. Reducing the frequency of General Practitioner visits is a good outcome in this rural area of limited health resources. Transdermal opioids are relatively simple and safe to use, both for prescribers and patients. As the population here ages, there will be an increased requirement for safe and effective pain relief for both degenerative and malignant pain. With the further development of these preparations, transdermal matrix opioids may open the door to the further relief of suffering and the living of fulfilled lives.

This study has filled a gap in the knowledge of the effective management of opioid treated CNCP patients in rural Tasmania. This may be applicable to similar rural areas in Australia and elsewhere, where healthcare resources are limited.

This thesis is presented as a series of published and submitted papers. Some repetition of text is unavoidable.

1 Persistent pain, opioids, and healthcare use in NW Tasmania

1.1 Introduction

‘Do transdermal (skin patch) opioids reduce healthcare use in a rural pain population?’

This question was asked at a presentation of the newly available transdermal preparation of buprenorphine (NorspanTM), during the 2006 Scientific Meeting of the Australian Pain Society. Physicians knew then that this route of delivery was as effective as the oral route in providing sustained analgesia (1). As this question would affect my work as a pain medicine physician in NW Tasmania, this question was worth addressing.

Persistent (non cancer) pain is increasing as the population ages, due mainly to the increase in spinal degeneration from osteoarthritis and osteoporosis (2). The more severe pains often respond to opioid medicines, and these may be the safest option (3). Patients with opioid responsive persistent pain utilise a variety of healthcare resources including general practitioner (GP), pain medicine, and pharmacy services. In rural areas, such as NW Tasmania, access to these services often involves significant travel, time, and financial burdens.

Traditionally, patients with opioid responsive persistent pain have been treated with oral opioid medicines of immediate and/or slow release effect (4). Many patients, particularly the elderly, have difficulty with opioid medicines and may require ongoing health-care support (5). In rural areas, this may be a significant burden for themselves and their families.

In 2005/6, two developments occurred in the availability of transdermal opioid medicines in Australia:

1 Buprenorphine transdermal matrix was introduced to the Australian market by Mundipharma P/L in three low dosages (5 µg/hr, 10 µg/hr, and 20 µg/hr), and became available through the Pharmaceutical Benefits Scheme (PBS) (1,6).

2 Fentanyl transdermal matrix was introduced to the Australian market by Janssen-Cilag P/L (replacing the previous reservoir preparations), and became available through the PBS (7). This range was expanded by the introduction of a lower dosage 12 µg/hr preparation (8).

Since then, the possibility of treating opioid naïve subjects safely with low dose transdermal opioid preparations has become a reality. Opioid medications are often difficult to manage, both for the patient and for the prescriber (9,10). The patient must keep to a regular dosing schedule, yet may experience unwanted

opioid effects. The prescriber must provide a safe and reliable means of providing the opioid medicine, whilst fulfilling all regulatory requirements (11). These factors, together with the underlying pain condition all have a part to play in healthcare use by this group of rural patients. If it is possible to reduce this burden by changing the route of opioid delivery, both patient and prescriber may benefit. This is the rationale for the present study.

1.2 Persistent pain

Persistent (chronic) pain is pain that persists longer than the temporal course of natural healing, associated with a particular type of injury or disease process (12). An understanding of persistent pain now includes the impact that the mind has in processing and interpreting pain signals.

The International Association for the Study of Pain (IASP) defines pain as ‘an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage’ (13). Pain is subjective in nature and defined by the person experiencing it. The term ‘chronic non-cancer pain’ (CNCP) is often used to describe all non-malignant persistent pain

From earliest times, pain was considered an injury/response phenomenon, which in classical times was documented as a ‘hard-wired’ mechanism (Figure 1.1).



Figure 1.1 Descartes' concept of the pain pathway (14).

In 1647, Rene Descartes wrote of the pain pathway: 'just as by pulling at one end of a rope one makes to strike at the same instant a bell, which hangs at the other end'. The advances in gross nervous system anatomy reinforced this concept in the eighteenth and nineteenth centuries.

In the twentieth century (following both the First and Second World Wars), increasing attention was focused on the treatment of persistent pain in injured war veterans. In 1961 the first multidisciplinary pain unit was established at the University of Washington School of Medicine, Seattle, led by John Bonica, an anaesthetist, who was instrumental in establishing the IASP. Increased multidisciplinary research into pain mechanisms soon bore fruit.

In 1965, Ronald Melzack, a Canadian psychologist, and Patrick Wall, a British physiologist, proposed the gate control theory of pain. Their theory asserts that activation of nerves that do not transmit pain signals (L) can interfere with signals from pain fibres (S) and inhibit an individual's perception of pain. This breaks away from the 'hard-wired concept' and opens up the myriad ways in which the experience of pain may be modulated (Figure 1.2).

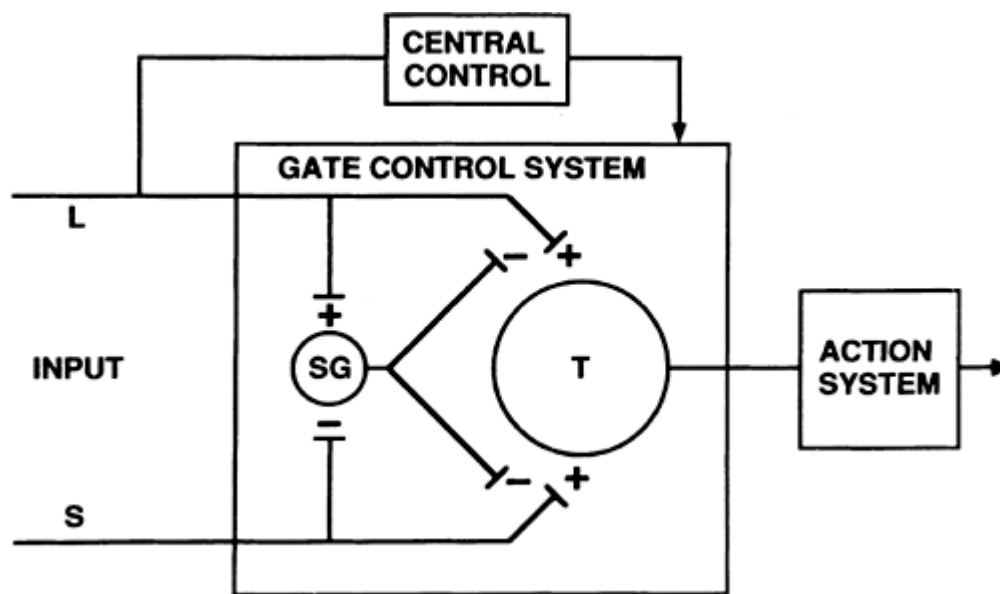


Figure 1.2 The gate control theory of pain (15).

To the gate control theory was added the conceptualising of persistent pain (onion skin) model advanced by John Loeser, a neurosurgeon. The noxious stimulus (nociception) leads to pain, which leads to suffering, which leads to pain behaviour (which may be observed). This concept provided a framework for the many aspects of persistent pain that are classed as pain behaviour (Figure 1.3).

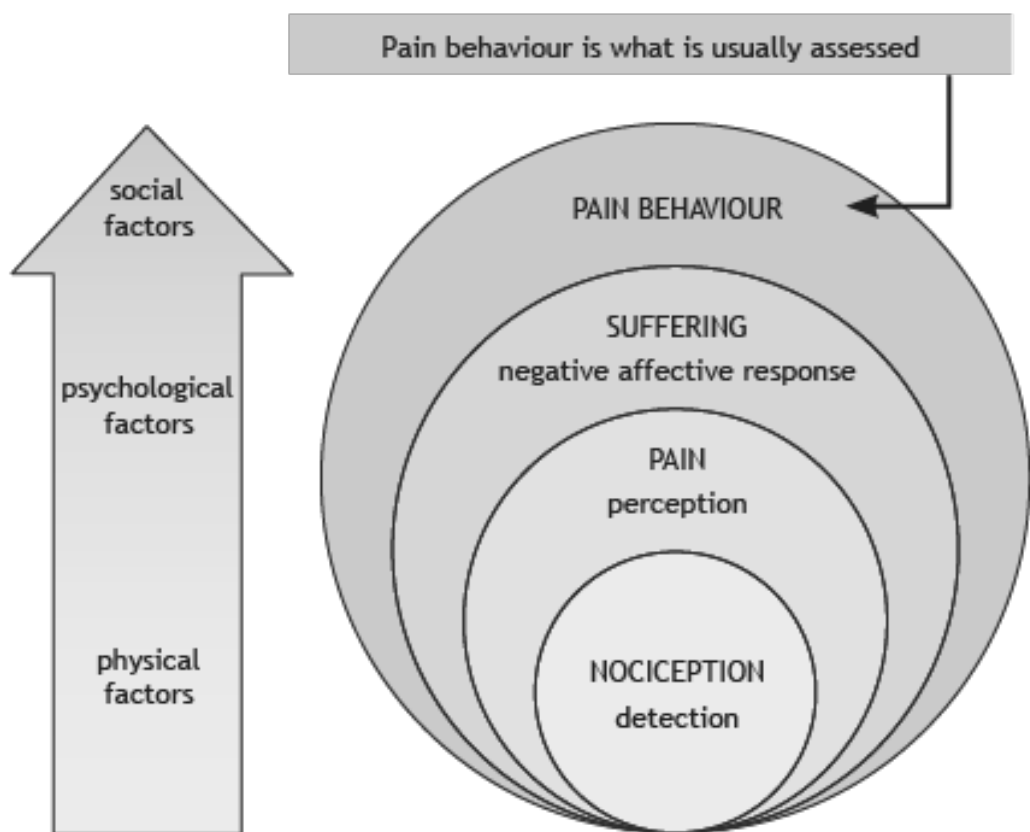


Figure 1.3 The conceptualisation of persistent pain (16).

It is this pain behaviour, in all its manifestations, that is the driver of health care use in persistent pain populations. Analgesic use (including opioid use) is but one aspect of the whole.

1.3 Opioid analgesics (opioids)

'Among the remedies, which it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium'

- Thomas Sydenham, 1624-1689

(English physician, and officer in the Parliamentary Army during the Civil War).

'The angelic face of opium is dazzlingly seductive, but if you look upon the other side of it, so much it will appear altogether a Devil. There is so such poison in this all-healing medicine that we ought not to be by any means secure or confident in the frequent and familiar use of it.'

- Thomas Willis, 1621-1673,

(English physician, and founding member of the Royal Society).

Opioids as opium, have been used for pain relief and for recreation for thousands of years. Originating from central Asia, their use spread along the great trade routes to China, South East Asia, India, the Middle East, Africa, and Europe. Thomas Sydenham praised God for the analgesic effect, but Thomas Willis warned of the dangers of recreational use.

Opioids in clinical use are primarily μ receptor agonists, active mainly in the central nervous system, but also on other tissues. Morphine, oxycodone, and

methadone, are commonly used as oral preparations, whilst buprenorphine and fentanyl are available as transdermal preparations.

The provision of pain relief was fundamental to the palliative care movement (17). In 1967, Cicely Saunders of the St Christopher's Hospice in London focused on rationalising the regular use of opioids in the care of the dying (18). Round the clock dosing of short acting opioids provided stable prolonged analgesia. This encouraged the development of longer acting opioid preparations (19).

The development of modified release oral opioids reached fruition in 1985 when the original MS ContinTM morphine preparation was marketed. The sustained release mechanism is a wax inside the tablet (not the coating on the outside) that when ingested, encases the released morphine sulphate.

Multidisciplinary pain clinics have since rationalised the use of opioid medications for the treatment of non-cancer pain (20). This began with Robert Portenoy in 1986 at the Sloan Kettering Cancer Center in New York (21). Many modified release opioids have since been developed, using both morphine and oxycodone.

In parallel with the development of modified release oral opioid preparations, the transdermal route has been pursued. These have transformed from the

original liquid reservoir fentanyl, to the modern matrix preparations of both fentanyl and buprenorphine.

1.3.1 Modified release and long acting orally administered opioid analgesics (oral opioids)

Modified release oral opioids are manufactured by combining a polymer, whether natural or synthetic, with the opioid in such a way that the opioid is released from the material in a pre-designed manner (22). This is usually adjusted to enable twice daily (12-hour) dosing regimens, which seem most convenient. These preparations are more commonly known as oral controlled release (OCR) opioids.

Some opioids have naturally prolonged duration of action due to prolonged half-lives (23). Buprenorphine and methadone are both examples, but only methadone is available via the PBS for persistent pain (oral buprenorphine is available for maintenance therapy for opioid dependency).

Morphine is an agonist at all opioid receptors, particularly the μ receptor. It is the prototypical opioid, and can be given via many routes of administration (24). After oral use, morphine is well absorbed; however, significant first-pass metabolism reduces the bioavailability to approximately 30% of the original dose. Oral administration results in a greater production of metabolites than parenteral administration. The metabolites comprise mainly morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). They are both excreted by the kidneys and accumulate in patients with renal impairment. M6G is a potent analgesic and contributes to the analgesic effect when morphine is given long term. M3G has no analgesic activity itself and may antagonise the

analgesic activity of morphine and be responsible for neurotoxic symptoms. The elimination half-life of oral morphine is 1.5 to 2 hours, and the duration of analgesic effect is 3 to 6 hours (25).

The oral route is preferred for long-term administration. In Australia, there are three modified release preparations of oral morphine available, MS Contin, MS MonoTM, and KapanolTM (26-28). MS Contin is formulated in an enteric-coated matrix tablet form (B) whereas MS Mono and Kapanol are formulated in a micro bead matrix capsule form (A) (Figure 1.4).

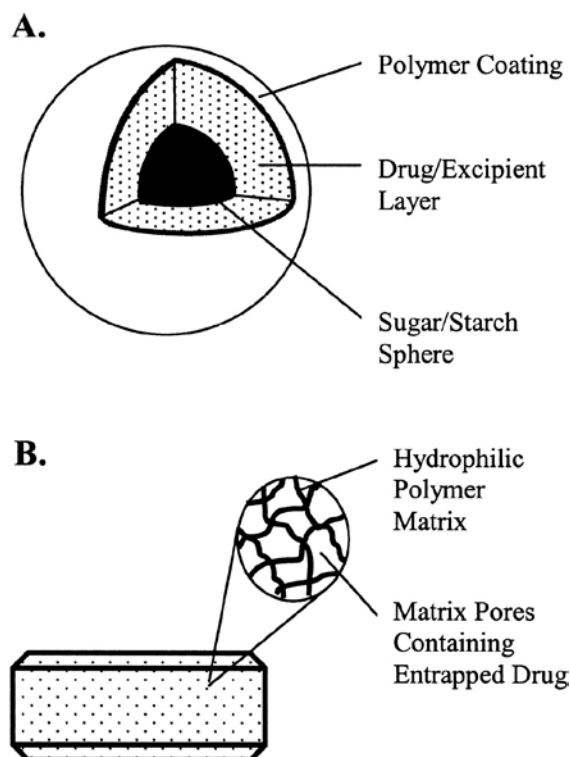


Figure 1.4 Representation of (A) an extended release bead formulation, and (B) a sustained release matrix tablet (22).

Oxycodone is up to two times as potent as morphine orally, because of its higher bioavailability (up to 90%). It is metabolised by CYP2D6 to oxymorphone, whose role in providing analgesia after a dose of oxycodone is thought to be limited (29). Efficacy of oxycodone is similar to that of morphine. OxycontinTM is a modified release preparation with a biphasic action. One third of the oxycodone is in the enteric coating and is immediately available. The remainder is within the matrix and is gradually released (30).

Methadone is a μ agonist with several features that differentiate it from most opioids. It has N-methyl-D-aspartate (NMDA) receptor antagonist activity (31). Persistent tissue damage generating neuropathic (nerve) pain can activate these receptors in the spinal cord, leading to hyperalgesia (central sensitisation). Its elimination half-life is biphasic and variable. This can cause problems with accumulation and toxicity (32).

Methadone has no active metabolites, an oral bioavailability of around 80%, high lipid solubility, and is relatively inexpensive. It is well absorbed orally and does not undergo extensive first-pass metabolism. There is marked individual variability in the half-life of methadone, between 15 to 60 hours has been reported. Methadone can be used twice daily for maintenance management of chronic pain (33).

1.3.2 Transdermally administered opioid analgesics (transdermal opioids)

Transdermal opioid matrix systems consist of a backing layer, an adhesive matrix layer with the opioid, and a removal foil on skin placement (Figure 1.5).

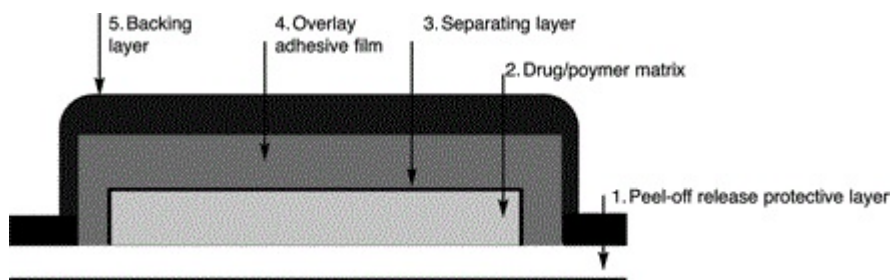


Figure 1.5 Cross-section through a matrix patch

When the skin is used as a port for drug delivery into the systemic circulation, there are several advantages compared to oral, sublingual, or parenteral administration. Since the gastrointestinal tract is by-passed, poor absorption or high hepatic first-pass metabolism can be avoided. The rate of drug delivery can be controlled and stable plasma levels achieved. This may improve long term analgesia and reduce adverse effects (34).

Buprenorphine is a partial agonist at μ opioid receptors and an antagonist at κ opioid receptors, with a prolonged duration of action (35). It is available as sublingual, parenteral and transdermal preparations. Buprenorphine is subject to considerable first-pass metabolism following oral administration.

Buprenorphine has high receptor affinity and slow dissociation from the receptor, with the analgesic effect persisting longer than the elimination half-life. The 7-day transdermal patch (Norspan™) reaches steady state after 3 days, and plasma levels decrease by 50% approximately 12 hours after the patch is removed (36) (Figure 1.6).

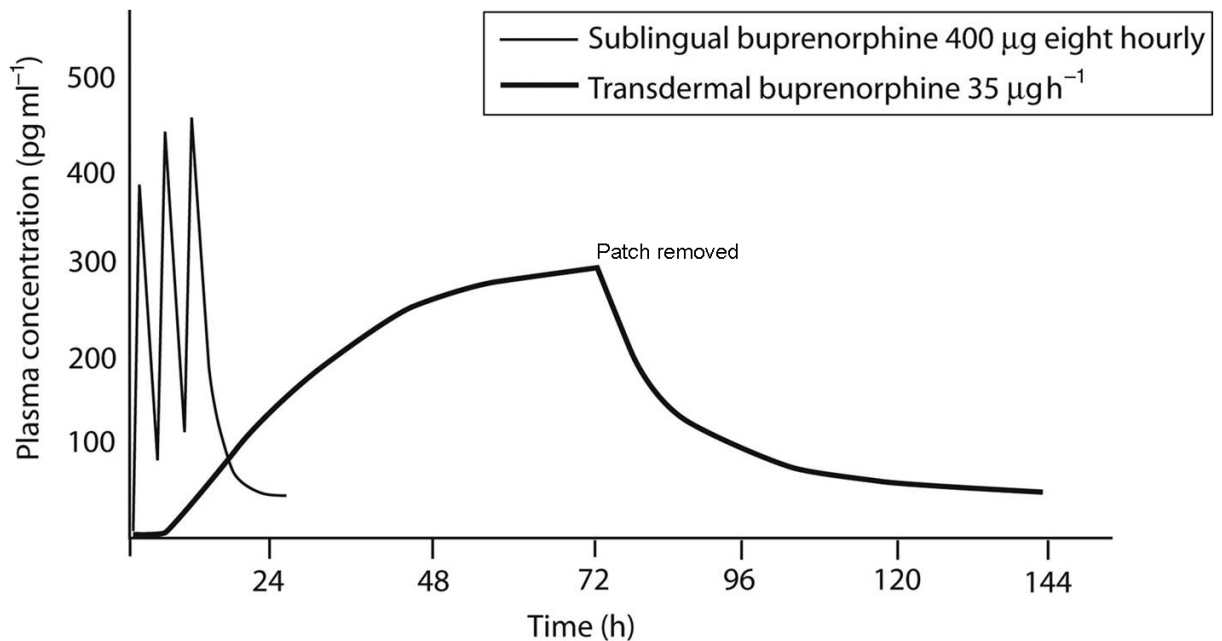


Figure 1.6 Comparison of plasma concentrations of buprenorphine after single application of 35 µg/hr patch (removed after 72 h) and sublingual dosing of 400 µg buprenorphine, eight hourly (37).

Fentanyl is a very potent synthetic opioid, with a short duration of action (38). It is used in both acute and chronic pain management. It can be administered via the oral mucosa (lozenge), parenterally (IM, IV, SC, intrathecal, epidural), transdermally (patch) and intranasally.

Fentanyl is metabolised in the liver to inactive products and is suitable for patients with renal failure. The three-day transdermal preparation (Durogesic™) reaches steady state after 24 hours and plasma levels decrease by 50% approximately 12 hours after the patch is removed (Figure 1.7).

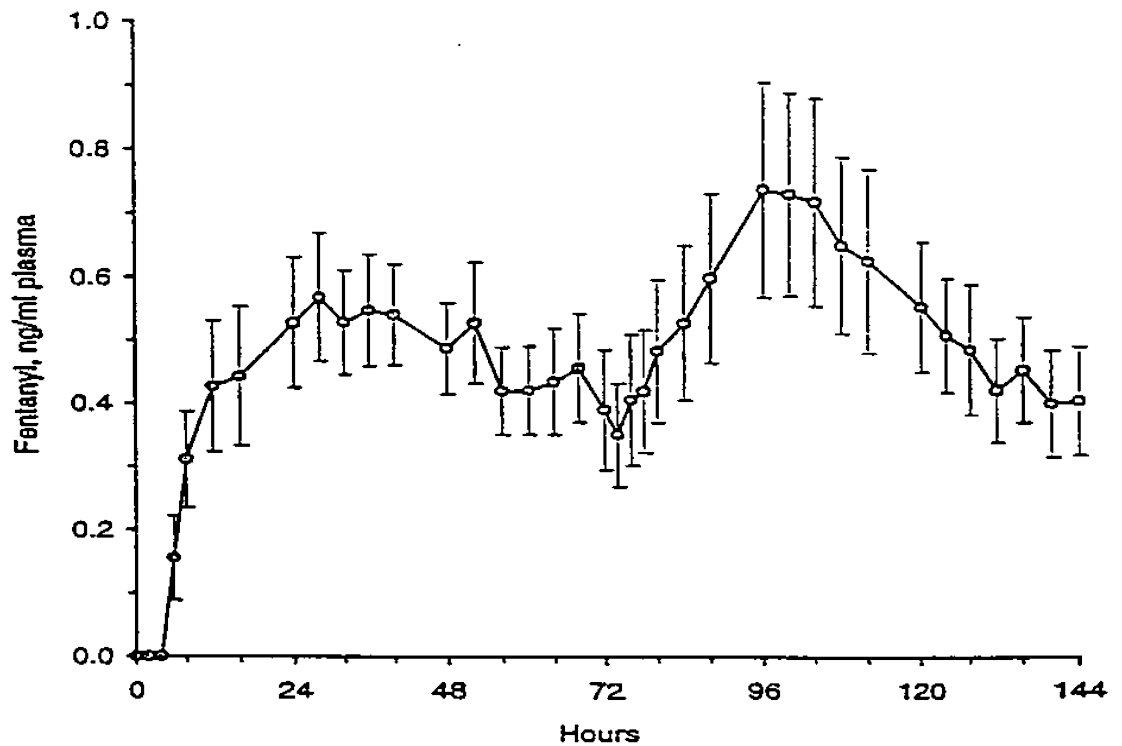


Figure 1.7: Mean serum concentration of fentanyl as a function of time after repeat 72-hour application of Durogesic 25 µg/hr (n=10) (39).

1.4 Healthcare use

People use healthcare when they perceive they have a health problem that needs fixing or managing. People with persistent pain are rarely 'fixed' and need significant managing of their pain morbidity and associated problems. Fixable persistent pain is usually large joint degeneration, treatable by replacement arthroplasty (40).

The vast majority of persistent pain is driven by degenerative musculoskeletal change of age or injury. The National Health Survey collects information on all long-term conditions particularly focusing on chronic diseases such as arthritis and osteoporosis, asthma, cancer, diabetes, heart and circulatory conditions, mental health and obesity.

In the 2007-08 survey, 15% of persons reported that they currently had arthritis; 13% of males and 17% of females (41). Of those with arthritis, 14% had rheumatoid arthritis and 51% had osteoarthritis. The proportion of people with arthritis increased with age from less than 1% of people aged less than 25 years to 48% of people aged 65 years and over.

Overall, 3% of persons had osteoporosis: 1% of males and 5% of females. Like arthritis, the proportion of people with osteoporosis increased with age, from less than 1% of people aged less than 25 years to 16% of people aged 65 years and over.

Of those who reported currently having arthritis / osteoporosis, 34% discussed management of their arthritis / osteoporosis with a GP or specialist in the last 12 months. It is this group, with more advanced disease, who may go on to pain management with opioid therapy (42).

A study of the 15 years from 1992 until 2007 (the start of this study) shows there has been a continuous increase in total opioid prescribing in Australia. with a rapid increase in the use of oxycodone. This study included tramadol, a weak opioid, which is not a controlled opioid. Transdermal fentanyl and buprenorphine became available as PBS medicines in 2006 and only fentanyl is recorded (Figure 1.8).

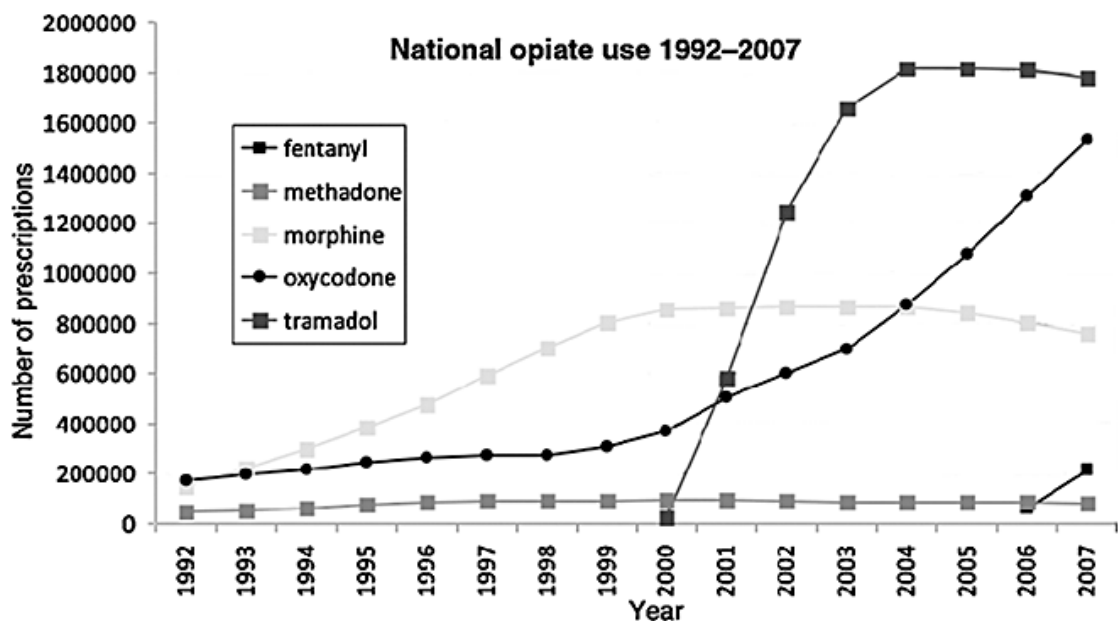


Figure 1.8 Number of PBS opioid prescriptions per annum 1992–2007 for fentanyl (2006), methadone, morphine, oxycodone and tramadol (2000) (43).

When looking at opioid prescriptions for CNCP patients in NW Tasmania, the situation differs. Data from the Pharmaceutical Services Branch (PSB) of the Department of Health for the first half of 2007, shows that morphine is the preferred OCR opioid medication for this group (Figure 1.9).

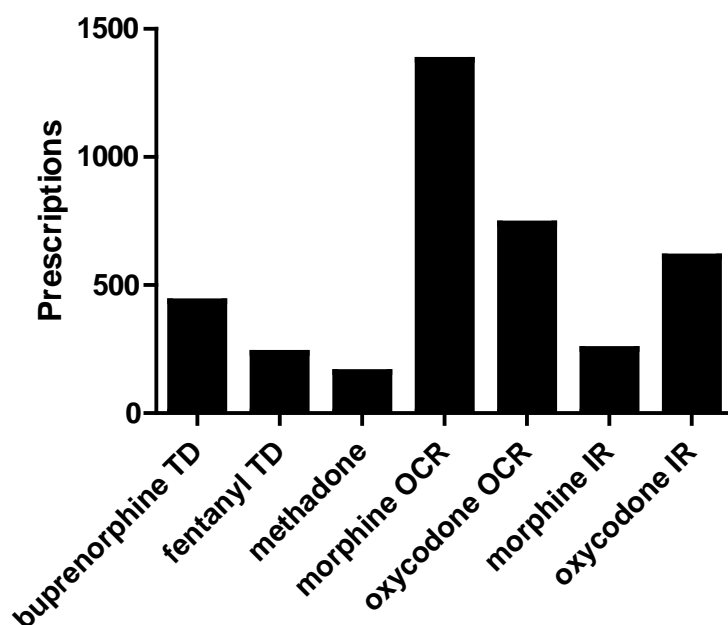


Figure 1.9 PBS opioid prescriptions dispensed in NW Tasmania during the first half of 2007 (excludes cancer / palliative care / nursing homes) (PSB internal data - Appendices 1.1, 1.2).

Abbreviations: TD, transdermal: OCR, oral controlled release: IR, immediate release.

Table 1.1 Adverse effects of opioids (44).

System	Adverse effects
cardiovascular	bradycardia due to stimulation of the vagal nucleus in the medulla histamine release by morphine and morphine analogues, postural hypotension from peripheral vasodilation and baroreflex inhibition
neurological	dose-dependent mental clouding, delirium, sedation, nausea and vomiting, cough suppression, miosis, respiratory depression or apnoea, excitatory phenomena with myoclonus with high doses relative to renal function,
dermatological	sweating, flushing urticaria and pruritus due to histamine release
gastrointestinal	vomiting, anorexia, decreased gastric motility, increased antral tone, delayed gastric emptying, slowed digestion, prolonged large bowel transit time, increased anal sphincter tone, constipation
neuroendocrine	hypothalamic effects (including inhibition of gonadotrophin-releasing hormone and corticotrophin-releasing factor) leading to decreased gonadotrophins, adrenocorticotrophic hormone, beta endorphin, testosterone and cortisol, and increased prolactin
respiratory	dose-related respiratory depression (which is more marked during sleep or with concomitant sedatives, hypnotics, and alcohol) bronchospasm due to histamine release
urinary	urinary retention and difficulty with micturition, increased external sphincter tone, decreased detrusor muscle tone, antidiuretic effect

1.4.1 Healthcare use literature

Throughout 2007, the scientific literature, particularly the resources of the National Library of Medicine (PubMed), Thomson Reuters (Web of Science) and Google Scholar, were searched for the Medical Subject Heading (MeSH) term 'Health Care Quality, Access, and Evaluation.' This concept is concerned with all aspects of the quality, accessibility, and appraisal of health care and health care delivery. Modifiers were then added, to reduce the recovery of texts focused on cancer, palliative care, substance abuse, and acute pain (surgical), to produce the final search criteria:

```
((("Health Care Quality, Access, and Evaluation "[Mesh] AND "Analgesics, Opioid") NOT "Neoplasms"[Mesh]) NOT "Substance-Related Disorders"[Mesh]) NOT "Surgical Procedures, Operative"[Mesh]) NOT "Palliative Care"[Mesh].
```

There was a paucity of studies of healthcare use by patients with persistent pain, who required opioid medication. There were none that compared OCR and TD opioid use directly.

A 2007 German study, entitled: 'utilisation of medical resources of patients with pain undergoing an outpatient opioid therapy', examined healthcare use, mainly from an economic perspective, using the German Federal Health Monitoring System (45). Fentanyl (reservoir) was the sole transdermal opioid studied. The authors conclude: 'The number of consultations rose significantly after the first prescription of opioids. Patients with chronic pain, who are treated with long-

lasting opioids for the first time, initially use considerably more healthcare resources. The type of opioid influences the amount of resource utilisation.'

The 2005 Danish study, entitled: '10-year follow-up of chronic non-malignant pain patients: opioid use, health related quality of life and health care utilization', reported on 160 opioid and non-opioid using persistent pain patients whose healthcare use was compared pre and post Multidisciplinary Pain Clinic (MPC) assessment (46). Their healthcare use peaked before MPC. Fentanyl (reservoir) was the sole transdermal opioid studied. The authors conclude that, 'health care utilization by chronic pain patients is very high and enormous medical and social resources are spent on these patients'.

There were no current prospective studies that examined this issue, solely from the opioid use point of view, comparing differing routes of administration, in a rural / regional area. This was the driver for the present study.

1.5 North West Tasmania

The North West of Tasmania, is defined by the Mersey-Lyell Statistical Division (SD) of the Australian Standard Geographical Classification (ASGC). This corresponds to the more familiar North West and West Coast of Tasmania Telephone Area Code (TAC) of 03 64xx xxxx. The region consists of nine Local Government Areas (LGAs) that are each identical to a Statistical Local Area (SLA), and have their associated Postal Areas (POAs) (Figure 1.10).

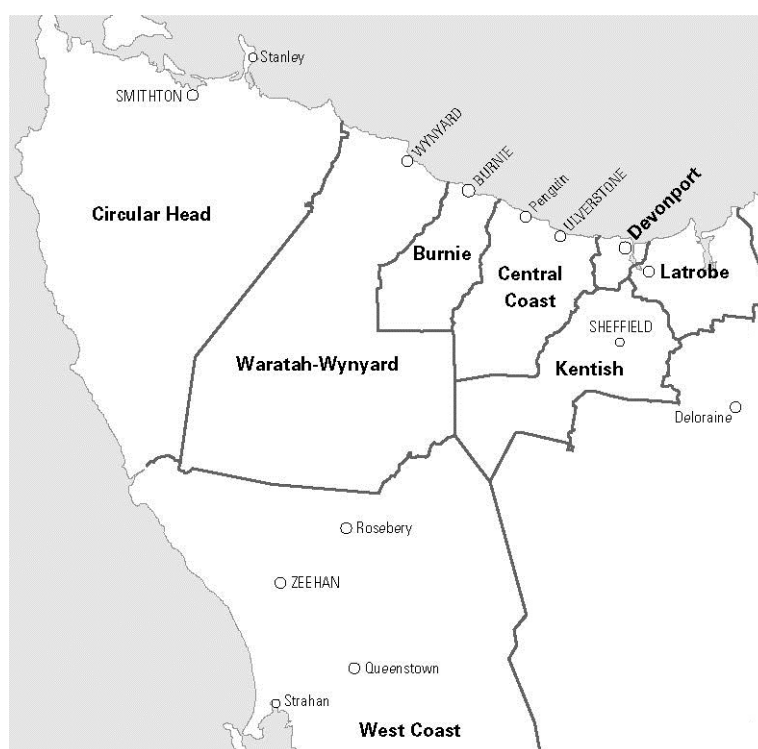


Figure 1.10 NW Tasmania LGAs of Latrobe, Kentish, Devonport, Central Coast, Burnie, Waratah-Wynyard, Circular Head, and West Coast.

This is a predominantly rural area with two centres of population, Devonport (east) and Burnie (central). The Tasmanian metropolitan areas of Launceston and Hobart are approximately two and four hours travel by road, respectively.

1.5.1 Regional and rural

The revised Accessibility / Remoteness Index of Australia (ARIA+) defines five categories of Remoteness Area (RA) based on road distance between populated localities and service centres.(47) These distances are used to generate an RA score for any location in Australia. This is available for a variety of geographical units including LGAs and POAs. ARIA+ forms the basis for the Australian Bureau of Statistics "Remoteness Structure" component of the ASGC (Table 1.2).

Table 1.2 Remoteness Area (RA)

Remoteness Area (RA)	ARIA+
0 - Major Cities	0 to ≤ 0.2
1 - Inner Regional	0.2 to ≤ 2.4
2 - Outer Regional	2.4 to ≤ 5.92
3 - Remote	5.92 to ≤ 10.53
4 - Very Remote	> 10.53

ARIA+ has been developed as an index (continuous variable with values between 0 and 15), based on a purely geographical calculation, in which remoteness is defined on the basis of road distance from any point to the nearest town (service centre) in each of five population size classes. The population size of the service centre is used as a proxy for the availability of a

range of services and road distance is used as a proxy for the degree of remoteness from those services.

The Mersey-Lyell Statistical Division is classified as 'remote' when compared to the Greater Hobart, Southern, and Northern regions (Figure 1.11) (Table 1.3).

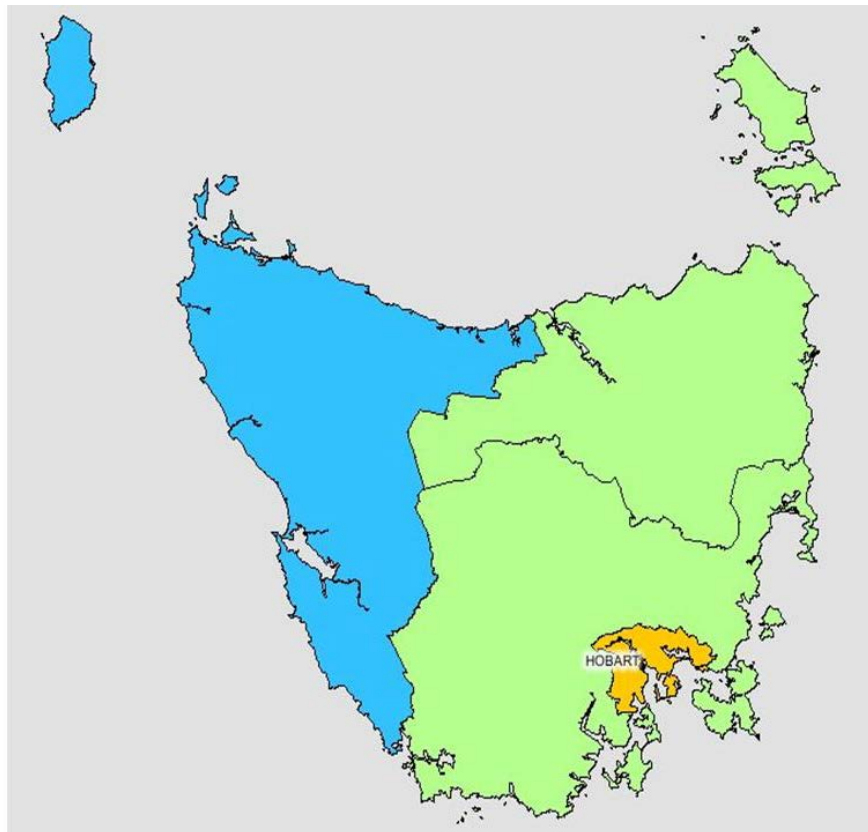


Figure 1.11 Tasmania SDs by RA (1=orange, 2=green, 3=blue).

Abbreviations: SD, statistical division: RA, remoteness area.

Table 1.3 Tasmanian SD data (48).

SD	TAC	POA(s)	Population (2008)	ARIA+ (2006)	RA
Greater Hobart	03 62xx xxxx	70xx	209300	2.22	1
Southern	03 62xx xxxx	71xx	36900	5.35	2
Northern	03 63xx xxxx	72xx	140300	5.15	2
Mersey-Lyell	03 64xx xxxx	73xx 74xx	111100	6.55	3

By RA classification, North West Tasmania is largely 'Outer Regional', with Circular Head and the West Coast being 'Remote', and King Island being 'Very Remote'. Even the population centres of Burnie and Devonport are 'Outer Regional'. The consequence of this is that for many of the region's population, travel distance and time may have a significant impact on access to health care (Figure 1.12) (Table 1.4).

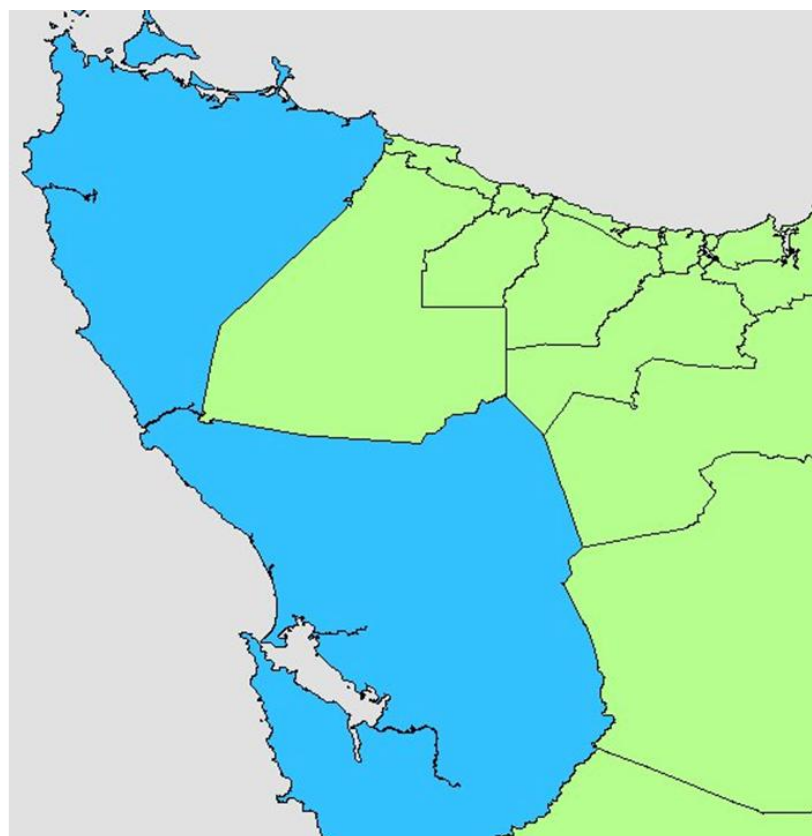


Figure 1.12 NW Tasmania LGAs by RA (2=green, 3=blue).

Abbreviations: LGA, local government area: RA remoteness area.

Table 1.4 NW Tasmania LGA data (49)

LGA	Main Centre	POA(s)	Population (2008)	ARIA+ (2006)	RA
Latrobe	Latrobe (rural)	7307	9329	2.53 2.96	2 2
Devonport	Devonport (rural)	7310	25208	2.5 2.69	2 2
Kentish	Sheffield	7305 7306	6130	3.96	2
Central Coast	Ulverstone (rural)	7315 7316	21571	2.69 3.57	2 2
Burnie	Burnie (rural)	7320 (7321)	19682	2.74 3.73	2 2
Waratah -Wynyard	Wynyard (rural)	7322 7325 (7321)	14022	3.25 5.23	2 2
Circular Head	Smithton	7330 7331 (7321)	8212	6.06	3
West Coast	Queenstown	7466 to 7470	5222	7.42	3
King Island	Currie	7256	1716	15	4

There is valid criticism of ARIA+ as an effective tool to guide health resource allocation, because 'purely geographical classifications alone cannot capture all relevant aspects of rural health service provision within a single measure' (50). The enhanced two-step floating catchment area (E2SFCA) method is an alternative tool for measuring access to healthcare resources within rural/regional areas. It assesses healthcare availability and population demand within travel time bands, and adjusts for the effect of distance (51). This has an Australian modification, as the Index for Rural Access, by incorporating a measure of health needs and mobility (52,53). However, throughout this study, ARIA+ has remained the Australian standard measure of Accessibility / Remoteness.

1.5.2 Socio-Economics

To assess the socio-economic status of the region, the 2006 Index of Relative Socio-economic Disadvantage from the Australian Bureau of Statistics (ABS) is used. This is derived from Census variables related to disadvantage, such as low income, low educational attainment, unemployment, and dwellings without motor vehicles.

These are scored, and given a decile place. Two thirds of NW Tasmania is at the third or lower decile, indicating that social mobility and access to health care may be difficult for many (Figure 1.13).

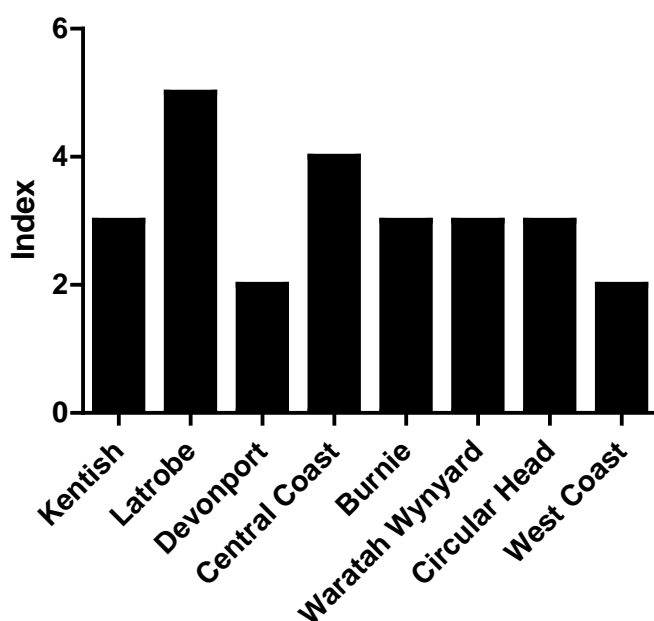


Figure 1.13 Index of relative socio-economic disadvantage (54)

(the lower the score, the greater the disadvantage).

1.6 Conclusion

The purpose of this study was to determine whether transdermal opioids reduce healthcare use in a rural pain population. To do this, the healthcare use of a NW Tasmanian pain population by their route of opioid administration will be compared. The choice between oral or transdermal administration of opioid medicines has only recently become available, hence the timeliness of this study.

Healthcare use is measurable. The vehicle used here was a prospective observational longitudinal study, which is described in the following chapter. This is a robust tool to answer these research questions:

For a chronic non-cancer pain population, in NW Tasmania, prescribed either oral or transdermal opioid analgesic medication...

- 1 Is there a difference in healthcare utilisation?
- 2 Is there a difference in the socio-economic costs involved?
- 3 Is there a difference in the use of 'breakthrough pain' medication?

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copyright or proprietary reasons.

Henshaw, J. S., 2011. Do transdermal opioids reduce healthcare use in an Australian rural pain population? A comparison with oral opioids, *Journal of opioid management* , 7(2), 135-144

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Henshaw, J. S., Walker, J., Geraghty, D., 2012.
Do transdermal opioids affect the personal
socioeconomic costs of healthcare access in
an Australian rural pain population? A
comparison with oral opioids, Journal of
opioid management 2012, 8(2), 126-132

4 The effect on additional analgesic use

4.1 Abstract

Objective: To determine the use of breakthrough immediate release opioids, and prescription only analgesics, with maintenance oral controlled release (OCR) and transdermal (TD) opioid treatment in a rural population with chronic non-cancer pain (CNCP).

Design: A longitudinal study measuring Pharmaceutical Benefits Scheme (PBS) recorded analgesic dispensed prescriptions (scripts) by route of maintenance opioid administration over time (monthly for one year). Subjects were opioid treated CNCP patients from North West Tasmania. The outcome measures of mean monthly immediate release opioid, and prescription only analgesic, scripts by route of maintenance opioid administration were analysed using generalised estimating equations with robust standard errors.

Results: The PBS details of 12191 dispensed scripts were obtained from 140 subjects over 12 months. Mean monthly immediate release opioid scripts with maintenance OCR opioids were 0.21 (95%CI 0.10 to 0.32). With TD opioids this was non significantly lower ($p=0.06$) at 0.04 scripts (95%CI 0.00 to 0.15). Mean monthly prescription only analgesic scripts with maintenance OCR opioids were 0.45 (95%CI= 0.28 to 0.62) and unchanged ($p=0.94$) for TD opioids at 0.46 (95%CI=0.21 to 0.72).

Conclusions: A trend towards reduced breakthrough immediate release opioid use, by TD opioid treated, compared to OCR opioid treated, CNCP rural patients was observed. Prescription only analgesic use is similar with both routes of maintenance opioid treatment. Sedative (benzodiazepine), and antidepressant use is also similar.

Modified content of this chapter has been accepted for publication by the Journal of Pain Research.

Henshaw JS, Walker, J, Geraghty,D The effect of transdermal opioid use on 'breakthrough' opioid and sedative prescribing for rural pain patients in North West Tasmania; a longitudinal study.

4.2 Introduction

This study measured the use of breakthrough immediate release (IR) controlled opioids and prescription only analgesics in an opioid treated CNCP population in NW Tasmania.

Prescription analgesics recorded were all non-controlled (Schedule 4 or 2) analgesics, including tramadol, codeine, paracetamol and NSAIDs, accessed through the Pharmaceutical Benefits Scheme (PBS) (91). Over the counter (OTC) medications were not recorded, as they are not PBS supplied medications and are freely available.

The aim here was to determine if subjects prescribed TD opioids had similar breakthrough IR opioid, and prescription only (S4) analgesic use, to those prescribed OCR opioids. Any benefit in reduction of healthcare activity gained by using TD opioids, would be negated, particularly with IR opioid increase.

The study additionally measured the co-prescribing of other neuroactive medicines, particularly sedatives (benzodiazepines) and antidepressants. Benzodiazepine use may increase opioid sedation, and their use between the TD and OCR opioid maintained subjects is compared.

4.3 Methods

This longitudinal study measured change in the subjects' PBS IR opioid, prescription only (S4) analgesic, sedative, and antidepressant, dispensed prescriptions over time (monthly for one year). Subjects were free to change their opioid medications (type, route, and dosage) throughout the study as prescribed by their treating doctor(s). The study was approved by the Human Research Ethics Committee (Tasmania) Network (approval number: H0009695) (Appendix 4.1).

In Australia, for individual patient use, Schedule 8 (controlled) OCR and IR opioids are dispensed in packs of 20, and similarly with Schedule 4 prescription only analgesics. TD opioids are dispensed for two weeks duration. Sedative and antidepressant medications are usually supplied for four weeks (92).

4.3.1 Subjects

Study subjects were recruited from the previous observational study at its completion (2010). The inclusion criterion was consent to access their PBS data for the most recently available calendar year (2008) (Appendices 4.2 – 4.4).

4.3.2 PBS data

This data provided, by subject, the date of supply and the PBS Item Code of each prescription issued. Coding, using the WHO Anatomical Therapeutic Chemical (ATC) classification system, enabled identification of the subjects'

controlled (opioid), non-controlled, and potential adjuvant analgesic prescriptions (93). The PBS item code was used to determine the route and preparation of the controlled opioid medications. Potential adjuvant analgesics were confined to neuroactive medications in the ATC N02C to N06A range (Table 4.1). All medicines were oral preparations apart from buprenorphine and fentanyl, which were transdermal.

Table 4.1 ATC codes and ATC names.

	ATC Code	ATC Name
Opioids (S8)	N02AE01	buprenorphine (TD)
	N02AB03	fentanyl (TD)
	N02AA01	morphine (OCR / IR)
	N02AC	methadone
	N02AA05	oxycodone (OCR/ IR)
Analgesics (S4)	N02AX02	tramadol
	N02AA59	codeine / paracetamol
Analgesics (S2)	N02E01	paracetamol
	M01A	NSAIDs
Sedatives (S4)	N05BA / N05CD	benzodiazepines
Antidepressants (S4)	N06AA	TCA
	N06AB	SSRI
	N06AX	SNRI

Abbreviation: ATC, anatomical therapeutic chemical

4.3.3 Statistical analysis

Longitudinal (panel) data consists of a panel variable and a time variable. Here the panel variable was the subject and the time variable was the prescription month. Monthly prescriptions were uniquely identified by these two variables.

The number of monthly IR opioid, analgesic, sedative, and antidepressant prescriptions by opioid group, were then repeatedly compared over the study period. The variation in monthly prescriptions within individual subjects over time was less than between subjects. This correlation was recognised and dealt with statistically.

The study outcome variables were mean monthly IR opioid (MIR), and analgesic (MA) prescriptions. The predictor variable was opioid group. The most frequent predictor characteristics were used to establish the reference mean MIR and MA (intercept). The change in mean MIR and MA (coefficient) which occurred if the predictor variable was present, the P value, and the 95% CI of this change were calculated.

4.4 Results

Of the 198 subjects who provided data to the observational studies previously described, 148 consented to the release of their associated PBS data. Four of these received their medications through the Department of Veterans' Affairs and four had ceased opioids. This provided 140 (71%) available datasets, with details of 12191 dispensed prescriptions for the study year (Appendices 4.5 - 4.8).

There were 3133 controlled (S8) opioid prescriptions of which 896 (29%) were TD, and 324 (10%) were IR. For this study, methadone was included in the OCR group, as twice daily dosing is recommended for CNCP therapy (44) (Figure 4.1).

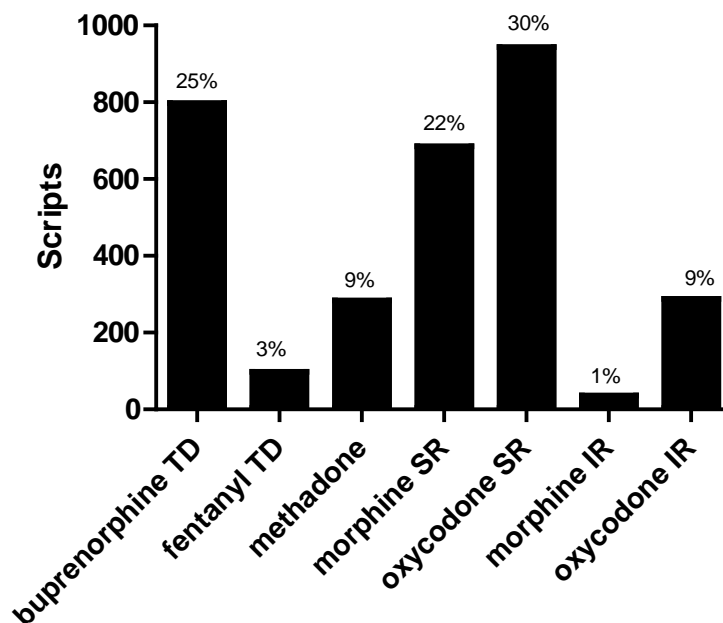


Figure 4.1 Controlled opioid scripts (n=3133).

Abbreviations: TD, transdermal: OCR, oral controlled release: IR, immediate release.

This produced 1433 subject months of data classified by opioid group. There were subjects who combined TD and OCR opioids and some who only received IR opioids. Of the 406 TD months, 15 (4%) were combined with IR opioids. Of the 848 OCR months, 111 (13%) were so combined (Figure 4.2).

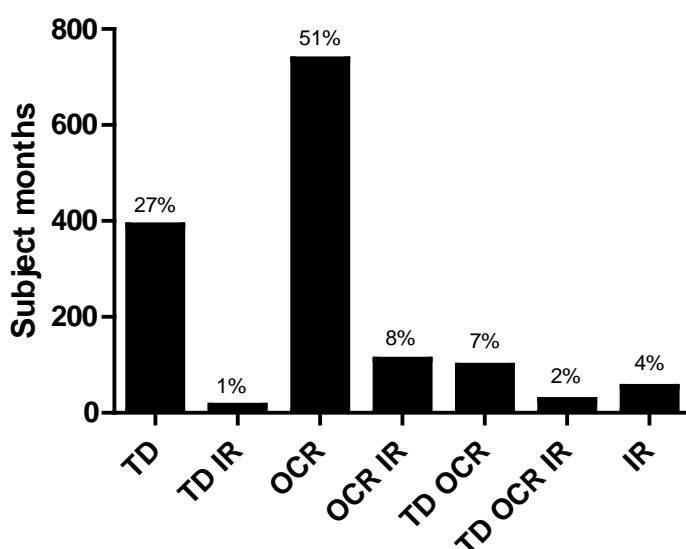


Figure 4.2 Opioid groups (n=1433).

Abbreviations: TD, transdermal: OCR, oral controlled release: IR, immediate release.

4.4.1 IR opioid use

The GEE population averaged model of mean monthly IR opioid scripts (MIR) adjusted for clustering on subjects was calculated. With OCR opioids, the subject would have 0.21 (95%CI 0.10 to 0.32) IR opioid scripts dispensed per

month. With TD opioids this was non-significantly lower ($p=0.06$) at 0.04 (95%CI 0.00 to 0.15) prescriptions (Table 4.2) (Figure 4.3).

Table 4.2 GEE population averaged model of mean monthly IR opioid scripts (MIR) adjusted for subject clustering (N=1379).

Predictor variable	Change in mean MIR	P	95% CI	n	%
Opioid Group					
(Reference OCR)				848	61
TD	-0.16	0.06	-0.34 - 0.01	406	29
TD OCR	0.02	0.89	-0.25 - 0.29	125	9
Reference OCR					
Mean MIR	0.21		0.10 - 0.32		

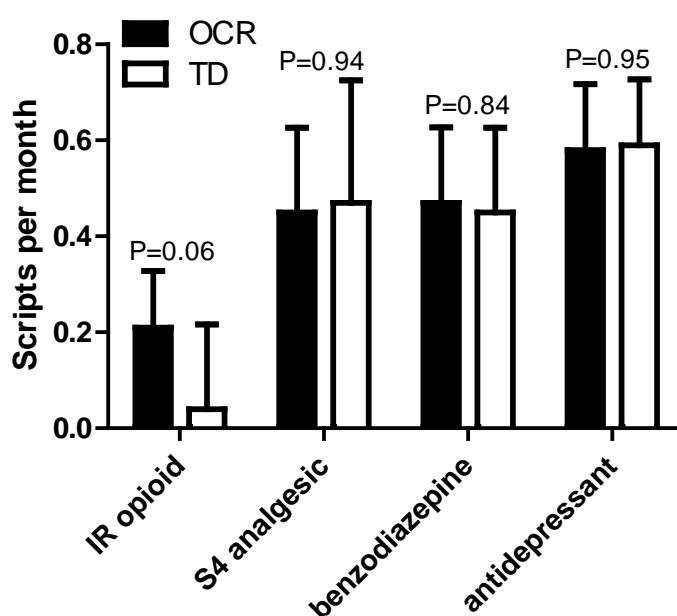


Figure 4.3 IR opioid, S4 analgesic, benzodiazepine, and antidepressant use (Mean, 95%CI, and P values)

4.4.2 Prescription analgesic use

There were 764 prescription only (S4) analgesic scripts dispensed, comprising the weak opioids tramadol and codeine, and the popular combination of codeine

with paracetamol. Additionally there were 907 scripts dispensed of the S2 analgesics comprising anti-inflammatory preparations and paracetamol. The extended release (ER) preparation of paracetamol accounted for 41% of paracetamol prescriptions (Figure 4.4).

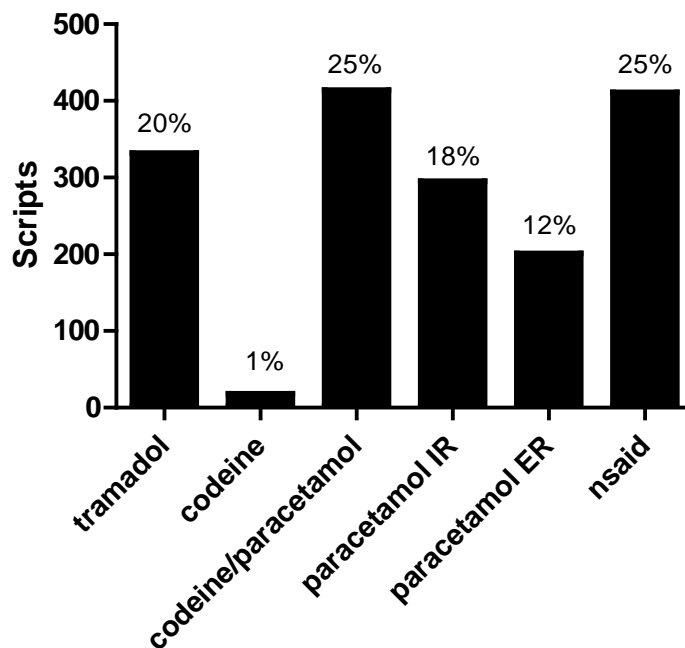


Figure 4.4 Analgesic scripts (n=1671).

The GEE population averaged model of mean monthly S4 analgesic scripts (MA) adjusted for clustering on subjects was calculated. Mean MA with OCR opioids was 0.45 scripts (95%CI= 0.28 – 0.62) and unchanged ($p=0.94$) for TD opioids at 0.46 (95%CI=0.21 – 0.72) (Table 4.3) (Figure 4.3).

Table 4.3 GEE population averaged model of mean monthly analgesic scripts (MA) adjusted for subject clustering (N=1433).

Predictor variable	Change in mean MA	P	95% CI	n	%
Opioid Group					
(Reference OCR)				737	51
TD	.01	0.94	-0.30 - 0.32	391	27
TD IR	.51	0.22	-0.31 - 1.33	15	1
OCR IR	.01	0.88	-0.12 - 0.14	111	8
TD OCR	.16	0.29	-0.13 - 0.45	98	7
TD OCR IR	-.02	0.92	-0.46 - 0.42	27	2
IR	-.20	0.31	-0.56 - 0.18	54	4
Reference OCR					
Mean MA	.45		0.28 - 0.62		

4.4.3 Sedative and antidepressant use

There were 796 benzodiazepine and 942 antidepressant prescriptions (Figure 4.5). Antidepressants were represented as tricyclics (TCA), and selective noradrenaline (SNRI) and serotonin (SSRI) reuptake inhibitors. Both TCAs and SNRIs have use in the treatment of neuropathic pain and may have additive analgesic properties when used with opioids (12).

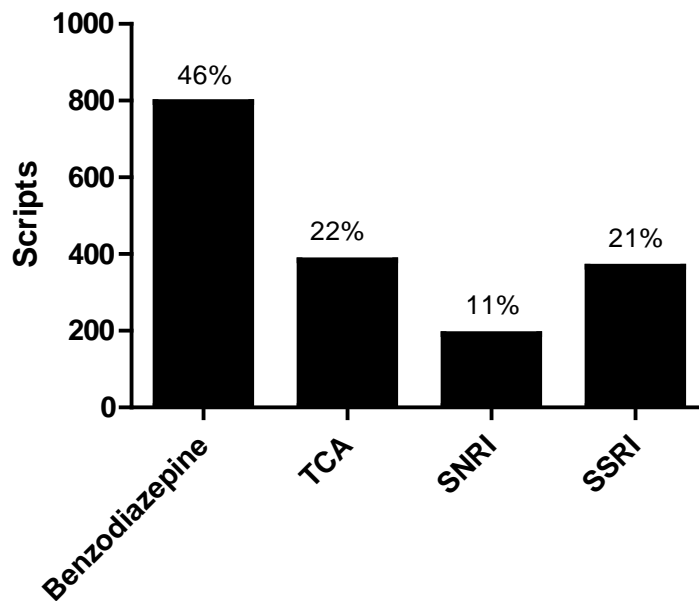


Figure 4.5 Benzodiazepine and antidepressant scripts (n=1738).

Abbreviations: TCA, tricyclics; SNRI, selective noradrenaline reuptake inhibitors; SSRI, serotonin reuptake inhibitors.

The GEE population averaged model of mean monthly benzodiazepine scripts and antidepressant scripts, adjusted for clustering on subjects was calculated. Mean monthly benzodiazepine scripts with OCR opioids were 0.47 (95%CI, 0.32 to 0.62) and unchanged ($p=0.84$) for TD opioids at 0.45 (95%CI, 0.28 to 0.62). Mean monthly antidepressant scripts with OCR opioids were 0.58 (95%CI, 0.45 to 0.72) and unchanged ($p=0.95$) for TD opioids at 0.59 (95%CI, 0.44 to 0.73) (Figure 4.3).

4.5 Discussion

This longitudinal study compared breakthrough IR opioid and prescription only analgesic use by opioid treated CNCP rural patients. We have shown that requirements for breakthrough IR opioids may decrease with TD opioid preparations. Although this result is not statistically significant ($P=0.06$), the 95% CI is largely negative. The rationale for use, and the provision of breakthrough opioid analgesia for CNCP patients is complex, both for patients and their prescribers (94).

The present study shows that use of prescription only analgesic medications by this group were similar for both TD and OCR opioids. Likewise, sedative (benzodiazepine) and antidepressant use were similar

This longitudinal study had inherent strengths and weaknesses. Being able to follow these categories of medication use by opioid treated CNCP subjects over twelve months with objective data recording through the PBS, was the major strength. Selection (recruitment) bias was the main potential weakness. Seventy five percent of the original study subjects were recruited for this subsequent study, with data from over twelve thousand prescriptions recorded.

We have shown previously in opioid treated rural patients that the use of TD opioid preparations, with their prolonged analgesic effect, significantly reduce GP contacts and may reduce total healthcare activity. We have also shown that

the personal time and expense involved in accessing this healthcare is equivalent. The prescribing of TD opioids may particularly benefit this group of pain patients in rural areas where there is a relative shortage of doctors (87). The present study reinforces this conclusion by demonstrating a trend towards reduced breakthrough IR opioid use with no additional prescription only analgesic, sedative, or antidepressant use by these subjects.

Prescribed analgesic use by opioid treated CNCP patients was a mix of weak opioids (tramadol and codeine) and non opioids (paracetamol and NSAIDs). There was frequent use of combination codeine/paracetamol medicines, which here accounted for one third of all prescribed analgesics. In Australia, there are currently no approved oxycodone/paracetamol preparations. These fixed combination medicines can make optimal paracetamol dosing complex for patients, and are incompatible with the extended release preparation.

OTC analgesic use was not recorded, and is a potential confounder. These medications, primarily aspirin, paracetamol, and the NSAID ibuprofen, are available at all supermarkets and corner stores. NW Tasmania is an area of low socio-economic index, and patients may seek to obtain most analgesics as subsidised PBS medications through their GPs (82).

There were three areas of pharmacotherapy potential concern. Firstly, the frequent use of sedative (benzodiazepines) medicines, which compound the sedation from the patients' primary opioids (95). Secondly, 20% of prescribed

analgesics were tramadol, despite the frequent use of antidepressants, raising the risk of serotonin toxicity (44). Finally, there was the risk of paracetamol toxicity by patients combining OTC paracetamol with prescribed fixed combination codeine/paracetamol (96).

4.6 Conclusions

This study from North West Tasmania showed that CNCP subjects maintained with TD opioids trend towards less breakthrough opioid medication. The use of prescription only analgesics, sedatives and antidepressants was equivalent to those maintained with OCR opioids. This may strengthen the case for more widespread use TD opioids in rural areas where healthcare access is often difficult. The continuing development of these systems is to be welcomed.

In the final chapter, the effect transdermal opioids have had on the areas of pain relief, drug diversion, and pharmaco-economics, are discussed. Some future developments for their use in North West Tasmania are outlined.

5 The benefits of transdermal opioids

5.1 Introduction

There is nothing new under the sun. Transdermal opioid patches for pain were used in Ancient Greece for sporting injuries (97). The Greek physician Galen (c. 129–200 BCE) makes particular reference to ‘Olympic Victor’s Dark Ointment’ (OVDO). He states that OVDO can be useful for treating extreme pain and swellings, forming one of the best eye salves (97). It was an opium-based treatment which forms a ‘patch’ when applied externally as an ointment, but still retains its elastic properties. When recreated using morphine as the opioid, OVDO ‘showed a transdermal transfer of morphine over time comparable to 25% of the most efficient modern transdermal opioid patches’ (98).

This study has demonstrated three possible benefits for rural/regional patients prescribed transdermal opioids for non-cancer pain (CNCP). First, there is a potential for less personal healthcare activity, particularly GP visits. Second, there is no increased socio-economic cost to bear. Third, there is potential for less need of ‘breakthrough’ opioid analgesia. Recent work has demonstrated a fourth benefit, the potential for increased compliance (99,100).

Opioid therapy for CNCP remains controversial due to concerns regarding long-term effectiveness and safety. The findings of a 2010 Cochrane Collaboration systematic review of 26 studies involving 4893 subjects ‘suggest that proper

management of opioids in well-selected patients can lead to long-term pain relief for some patients' (101). The review reported that both OCR and TD opioids were effective in pain relief, but TD opioids were less likely to be discontinued due to adverse effects or poor analgesia (Figure 5.1). They are, potentially, a more attractive option for rural patients and prescribers.

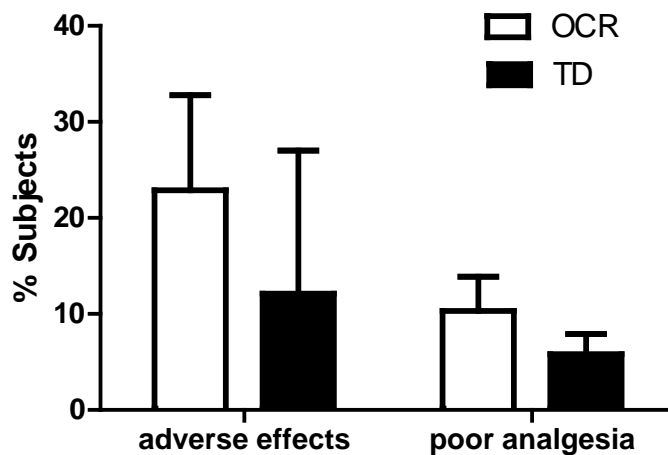


Figure 5.1 Reasons for ceasing opioid treatment for CNCP (mean and 95%CI) (101).

5.2 Pain relief

We know that TD opioids are as effective as OCR opioids in the treatment of persistent pain. What are the barriers to their more widespread use? Prescriber familiarity and patient acceptance are probably the main issues.

Doctors are very familiar with morphine and oxycodone. They are the main pillars of acute pain management in hospitals and in the community. Morphine is used parenterally, and oxycodone is used orally. Their dosing, administration, and adverse effects are well known. Because of this, their use as OCR medications is relatively straightforward. Additionally, these preparations have been available for more than twenty years with an extensive range of dosages available (26,28,30).

Currently available TD opioids are either buprenorphine or fentanyl. Buprenorphine is well known to addiction medicine doctors for its use in the treatment of opioid dependence. Fentanyl is used frequently for short acting analgesia in anaesthesia and intensive care. However, outside of these circles, their use was very limited. Hence, until the availability of their TD preparations in 2005/6, most doctors were unfamiliar with the clinical use of these opioids (43). The dosage ranges available in Australia. are limited, with buprenorphine being available at lower, and fentanyl at higher, morphine equivalence (36,39). If analgesic requirements change markedly, the opioid has to be changed as well. This can be a complex task.

Patients realize that opioid medications, as with all medications, may have adverse effects. Pain relief from TD opioids is equivalent to that from oral opioids and adverse effects are potentially less. There is one issue relevant to all TD medications, but especially prominent with the TD buprenorphine preparation NorspanTM, that of skin irritation (102). All skin occlusive patches may produce skin irritation. If this is not a sensitivity reaction to the patch components, then it is the area of cover and the duration of administration, that drives this irritation. Even with site rotation, this may be a sufficient adverse effect to cause loss of compliance. Norspan preparations are large and are applied for seven days (Appendix 5.1). The TD fentanyl preparations DurogesicTM are small, and are applied for three days.

These difficulties are readily surmountable in two ways. Firstly, prescriber therapeutic medical education is currently being provided by the National Prescriber Service (NPS). This provides an evidence-based guide to the therapeutic management of opioid therapy for CNCP patients. Prescribers may have confidence that their opioid prescribing practice is effective and current. Secondly, pharmaceutical companies are developing an increased range of TD opioid products. Higher dose ranges of TD buprenorphine with three day application are becoming available, and lower dose ranges of TD fentanyl are being developed (103). In the near future, prescriber familiarity and patient acceptance of TD opioid preparations should match that of the OCR opioid preparations.

With these developments, it may be possible to offer the benefits of TD opioid administration to patients with neoplastic disease. Due to the fluctuating nature of neoplastic pain and the limited range of TD opioid dosages, these patients have been managed with background OCR opioids and 'breakthrough' immediate release (IR) opioids. Neoplastic disease is more prevalent in the community due to increased survival and the aging population. Development of effective pain relief for these patients would be expanded, by the addition of TD opioid therapy to the mix.

5.3 Diversion

All opioid analgesics approved by the TGA and available to patients via the PBS are Schedule 8 medications. They incur an additional layer of regulatory control above Schedule 4 prescription only medications. This is primarily to prevent diversion to the community for non-therapeutic purposes.

OCR opioids are readily diverted. The Tasmanian Drug Trends (2011) report of the National Drug and Alcohol Research Centre (NDARC) found that for injecting drug users (IDUs), heroin was difficult to access (104). MS Contin remained the predominant (morphine) preparation, and OxyContin tablets were the predominant (oxycodone) formulation' that were diverted for non-therapeutic purposes

TD matrix opioid preparations are not mentioned by the IDUs included in this study. They may be diverted and the opioid may be injected, but with matrix preparations, this is a non-trivial task. The New Zealand Drug Intelligence Bureau concluded: 'the buprenorphine transdermal patch, is not considered to be of significant potential for diversion or misuse for illicit purposes, whilst the NDARC found: 'diverted fentanyl does not yet appear to pose a major threat to IDUs in Australia' (105,106). The 2012 Tasmanian Police Corporate Performance Report indicates a substantial increase in seized oral opioids and benzodiazepines in NW Tasmania, with evidence that 'some individuals are

legitimately obtaining prescription drugs and then on-selling them or trading prescription drugs for other drugs or property' (107) (Figure 5.2).

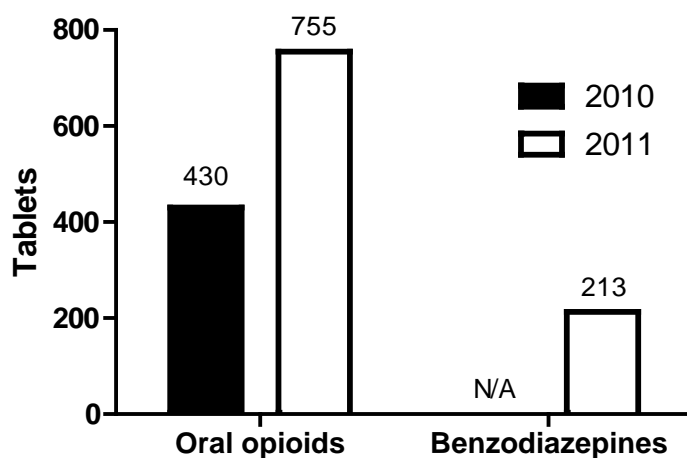


Figure 5.2 Seized prescription oral opioids and benzodiazepines in NW Tasmania (2010 and 2011).

If the risk of opioid diversion is a consideration in prescribing for CNCP patients then, at present, TD opioids are the safer option. If this leads to a reduction in the prevalence of opioid diversion in NW Tasmania, there are considerable economic benefits, both from a reduction in self-harm, and from drug enforcement costs.

5.4 Pharmacoeconomics

The term 'pharmacoeconomics' refers to the comparative study of the value of one pharmaceutical drug therapy to another. It is a part of health economics. In this study, we were concerned with the comparison of OCR versus TD opioid therapy for CNCP in the context of rural and regional North West Tasmania.

We have shown that TD opioids potentially reduce overall healthcare use and do reduce GP contact. We know that there is no patient socio-economic burden in achieving this. The use of 'breakthrough' IR opioids is potentially reduced, and there is no concomitant increase in prescription analgesia, sedative, or antidepressant use. Additionally, patients are more compliant with TD opioid dosing, and there is currently no evidence that in Tasmania, there is diversion to IDUs.

Although this was not the prime focus, our results suggest that from a holistic pharmacoeconomic view, TD opioids are superior to OCR opioids in the context of this study. NW Tasmania is not unlike other rural and regional areas of Australia, and these results may well be applicable more widely.

5.5 Future research

This study has not examined the therapeutic implications of using transdermal versus oral routes of administration for these opioid analgesics in this population. To do so requires knowledge of the effectiveness of these medicines in alleviating daily pain, and in increasing the activities of daily living. In my view, this may require the multi centre cooperation of rural pain units to provide the necessary research resources.

There remain many gaps in our knowledge of the effective use of opioid analgesics in maintenance of CNCP rural patients. These are not static targets, as both the populations and the opioid medications develop.

Aging is the primary change in this population. The 'Baby Boomer' cohort is beginning to feel its age. They are developing the same painful degenerative musculoskeletal changes as their parents, perhaps without the same stoic philosophy. This will place a particular burden on future healthcare provision of effective pain relief.

Opioid medications are changing. The lower dose ranges of both OCR and TD opioids have been expanding, providing more flexibility in managing the elderly and infirm. The addition of low dose opioid antagonists to OCR preparations is increasingly being used to mitigate against medication diversion (108)

The aim, as always, is to provide the most effective outcomes for rural pain populations, where resources will always be limited. This study is but one-step in that direction.

5.6 Conclusion

'Peter' is a retired farmer who lives with his wife outside of Sheffield, the nearest town to Cradle Mountain National Park. He had been physically active for all his working life, but was eventually forced off his land by significant painful spinal degeneration, which made tractor driving unbearable. He has had diabetes and hypertension for many years, which precluded regular anti-inflammatory use. By 2005, his GP decided that Peter might benefit from low dose opioid medication to manage his pain, and improve his mobility. A trial of oral MS Contin helped, but, in spite of instructions, he would only take them if his pain was unbearable. However stubborn Peter may have been, his GP was his match. In the winter of 2006, she trialled him with the newly released buprenorphine weekly patch, which the practice nurse trained Peter's wife to apply correctly. Peter still uses these patches, he is mobile around the house and garden, and his joy is his great grandchildren.

In 2006, Peter's GP knew that transdermal opioids were as effective as oral opioids of equivalent dosage. She did know what effect using these medicines would have on overall healthcare activity for her patients. This study has shed some light on this issue, by following the journey of 198 men and women like Peter.

Between 2007 and 2010, these study subjects provided 1804 monthly diary pages of their out-of-home healthcare activity, detailing 10564 individual

healthcare contacts. From this data, a picture of the healthcare activity of opioid treated persistent pain patients throughout NW Tasmania emerged.

This longitudinal study compared healthcare activity by patients using oral or transdermal opioids. There is a personal socioeconomic cost involved accessing healthcare, more so in rural areas. Pain patients may use additional analgesics with their opioids. These related issues were assessed, as any benefit from reduced healthcare activity would likely be lost if patient costs, or their need for additional analgesics, increased.

GP contacts were reduced significantly, and there was a trend towards less total healthcare activity, by patients using transdermal opioids. Their personal socioeconomic costs involved remained unchanged. Additional analgesic use was unchanged, but there was a trend towards reduced use of short acting opioids for 'breakthrough' pain. Whether some patients have individual characteristics that enhance their response to the 'steady state' delivery of opioid medication by the transdermal route is currently unknown.

In NW Tasmania, transdermal opioids do seem to offer a benefit to patients compared to oral opioids. Reducing the frequency of GP visits is a good outcome in this rural area of limited health resources.

Transdermal opioids are relatively simple and safe to use, both for prescribers and patients. As the population here ages, there will be an increased

requirement for safe and effective pain relief for both degenerative and malignant pain. With the development of these preparations, transdermal matrix opioids may open the door to the further relief of suffering and the living of fulfilled lives.

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